Fetoscopic Laser Therapy for Twin–Twin Transfusion Syndrome

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SUMMARY

Twin–twin transfusion syndrome (TTTS) complicates approximately 1 in 5 of all monochorionic, diamniotic twin pregnancies. If of early onset and untreated, severe TTTS is associated with a dismal prognosis, with perinatal mortality rates exceeding 90%. The most controversial issue regarding the optimal treatment of TTTS has centered on the use of amniocentesis or laser until the first and only randomized trial on interventions for TTTS was published a couple of years ago, comparing laser to amnioreduction. That report confirmed that the laser group had a higher likelihood of the survival of at least one twin to 28 days of age and to 6 months of age. Infants in the laser group also had a lower incidence of cystic periventricular leukomalacia and were more likely to be free of neurologic complications at 6 months of age (52% *vs.* 31%, $p=0.003$). Although not every case of TTTS is an eligible candidate for fetoscopic-guided laser therapy, it is recommended that obstetricians who have the chance to manage TTTS in their daily practice be familiar with the rationale behind this laser treatment for TTTS. [*Taiwanese J Obstet Gynecol* 2006;45(4):294–301]

Key Words: amnioreduction, fetoscope, laser therapy, twin–twin transfusion syndrome

Introduction

Twin–twin transfusion syndrome (TTTS) complicates approximately 1 in 5 of all monochorionic, diamniotic twin pregnancies [1]. TTTS could also affect triplet or higher order multiple gestations, in which at least two fetuses are monochorionic [2,3]. In monoamniotic twins, the lack of a dividing membrane precludes the combined presence of polyhydramnios and oligohydramnios. In these patients, the syndrome can be suspected by the presence of polyhydramnios and differences in bladder filling of the two fetuses [4].

The etiology of TTTS appears to result from a net unbalanced flow of blood between two monochorionic fetuses through placental vascular communications, which results in a donor twin and a recipient twin. Although actual documentation of the unbalanced blood flow remains elusive [5], vascular anastomoses might be responsible for the development of TTTS if the vascular design is such that it forces a net flow from donor to recipient [5]. Alternatively, vascular anastomoses might play a passive role in the development of the syndrome, but nonetheless allows its development. This is the case with monochorionic twins who are discordant for congenital heart disease, cardiomyopathies, cord anomalies, or other conditions associated with uneven hemodynamic competence [4].

When the onset of this condition occurs before 26 weeks of gestation, there is a significant associated risk of fetal loss, perinatal death, and subsequent handicap in survivors [6]. If untreated at its early onset, severe TTTS has a dismal prognosis, with perinatal mortality rates >90% [7], and >30% of survivors suffering from associated neurodevelopmental anomalies [8].

The poor outcome of untreated TTTS has led to the introduction of a number of treatments. Most of them, however, are subject to controversy. Amnioreduction and endoscopic laser ablation of vascular anastomoses have both been shown to reduce perinatal mortality in an uncontrolled series [9]. Nevertheless, which is the

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optimal treatment for TTTS, serial amniocentesis or laser, has long been an issue of debate [4].

Amnioreduction is a relatively simple and widely available treatment that involves repetitive percutaneous removal of large volumes of amniotic fluid (usually in excess of 1–2 L on each occasion). The rationale for this technique is to prevent preterm labor related to hydramnios. The rationale for endoscopic laser coagulation is to interrupt the placental vascular communications between the twins on the chorionic plate, a technique advocated in a few specialist centers [6]. The argument over which treatment is superior lasted for years until the first and only randomized trial on interventions for TTTS was published, comparing laser to amnioreduction [10]. It was proven that the laser group had a higher likelihood of the survival of at least one twin to 28 days of age (76% *vs.* 56%; relative risk of the death of both fetuses, 0.63; 95% confidence interval, 0.25–0.93; $p = 0.009$) and to 6 months of age ($p = 0.002$). Infants in the laser group also had a lower incidence of cystic periventricular leukomalacia (6% *vs.* 14%; $p = 0.02$) and were more likely to be free of neurologic complications at 6 months of age (52% *vs.* 31%; $p = 0.003$). This study demonstrated that fetoscopic-guided laser ablation of chorionic plate vascular anastomoses was a more favorable choice as a first-line treatment for severe TTTS diagnosed before 26 weeks.

It has been recognized that laser surgery for TTTS should be available in fetal medicine units that are managing at least 20 cases per year [9]. The incidence of monozygotic twins is constant at 4 per 1,000 births [11]. Currently in Taiwan, with an estimated 200,000 births per year, 800 sets of monozygotic twins are expected to be delivered, with 80 cases of TTTS predicted to occur each year. It is, therefore, recommended that obstetricians be familiar with the diagnosis of TTTS as well as the indications, procedures and the complications of laser treatment for this disorder.

History of Fetoscopic Laser Therapy for TTTS

The basic technique was pioneered by De Lia in the 1980s. In 1983, De Lia saw a case of TTTS at 23 weeks' gestation and treated the mother with digoxin [12]. Both fetuses eventually survived, but the hydropic recipient twin was later found to be affected with cerebral palsy. After examining the placenta, De Lia found that only a single arteriovenous anastomosis existed between the two involved fetuses on the placenta. At that time, he came up with the idea that if he could block the single arteriovenous anastomosis, he might be able to treat the disease. He then began a series of experiments with a sheep model using a YAG laser [13]. Eventually, his group performed the first laser treatment in 1988 [14], a procedure known as fetoscopic laser occlusion of chorioangiopagus vessels (FLOC).

The second person who contributed to the development of this technique is Ville. In the original description of FLOC by De Lia et al [14], laparotomy was performed under general or regional anesthesia to explore the uterus, followed by insertion of an endoscope into the amniotic cavity. Ville, on the other hand, performed laser therapy for TTTS via a percutaneous approach using a 2.0-mm fiber-optic endoscope without resorting to laparotomy, thereby making the technique less invasive [15]. According to De Lia et al, the identification of the target vessels for coagulation was based on their endoscopic appearance [14]. The described technique was perceived by other investigators to be difficult, perhaps due to the lack of distinct anatomical landmarks or accurate knowledge of placental anatomy [4]. Ville et al suggested using the dividing membrane as the landmark to identify the communicating vessels [15], and that all vessels of the donor twin crossing the dividing membrane into the sac of the recipient twin should be photocoagulated. This approach was easier to understand since the membrane that separated the fetuses would also serve as a landmark that divided the placenta.

Finally, we should mention Quintero who proposed the staging classification of TTTS that is now used worldwide [16]. In addition, Quintero devised a technique called selective laser photocoagulation of communicating vessels (SLPCV) [17]. SLPCV selectively coagulates communicating vessels and preserves the non-communicating vessels even if they cross the dividing membrane. In Ville et al's description [15], the advantage of coagulating all of the donor vessels crossing the dividing membrane was to set up a standard using the dividing membrane as an anatomical landmark reference, thus improving its reproducibility. However, this nonselective ablation of all the crossing vessels has been shown to increase the likelihood of dual intrauterine fetal death in comparison to SLPCV [18]. In Quintero et al's description of SLPCV [17], each placental artery is followed to its terminal end in the placenta (arteries cross over veins), and a returning vein from that cotyledon should be traced draining back to the same twin. If blood is drained to the other twin, then a deep arteriovenous anastomosis is present. Arterioarterial or venovenous anastomoses are identified easily by noting lack of a terminal end for an artery or a vein, respectively. SLPCV is associated with an 85% success rate (likelihood that at least one fetus survives) and a 3–5% risk of cerebral palsy. SLPCV compares favorably with the previous nonselective technique, resulting in a lower rate of dual fetal demise (5.6% *vs.* 22%) [18]. Reliable techniques to treat patients with anterior placentas have also been developed by Quintero et al [19].

In the following sections, this article will focus primarily on introducing the technique as developed by Quintero et al, who have performed over 500 cases at the Florida Institute for Fetal Diagnosis and Therapy at St Joseph's Women's Hospital from 1996 to 2005. Recently, in November 2005, Dr Quintero joined the University of South Florida as professor and director of the division of maternal–fetal medicine in the department of obstetrics and gynecology there.

Diagnosis of TTTS

About 25% of cases transferred to the Florida Institute for Fetal Diagnosis and Therapy with the suspected diagnosis of TTTS later turned out not to fulfill the TTTS criteria. Those cases varied from simple amniotic fluid volume discordance to isolated polyhydramnios and isolated oligohydramnios [4].

The diagnosis of TTTS is based on the following sonographic findings: (1) polyhydramnios, ≥ 8 cm of maximum vertical pocket (MVP) in the recipient twin; (2) oligohydramnios, MVP ≤ 2 cm in the donor twin; (3) single placenta, thin dividing membrane, and similar external genitalia.

In a study by Danskin and Neilson of 178 twin pairs [20], only four pairs had a hemoglobin difference > 5 g/dL and a weight difference > 20%, and none of those pregnancies showed evidence of polyhydramnios or oligohydramnios. Similarly, percutaneous umbilical blood sampling in six TTTS patients failed to show hemoglobin differences > 5 g/dL, except in one pregnancy [21]. Consequently, the previous pediatric criteria of a hemoglobin difference > 5 g/dL and a weight difference > 20% are no longer applicable [4].

The most widely used criteria for TTTS staging is that of Quintero et al [16], and is as follows:

- Stage I—the bladder of the donor twin is still visible, and Doppler studies are still normal;
- Stage II—the bladder of the donor twin is not visible (during the length of the examination, usually 1 hour), but Doppler studies are not critically abnormal;
- Stage III—Doppler studies are critically abnormal in either twin and are characterized as absent or reverse end-diastolic velocity in the umbilical artery, reverse flow in the ductus venosus, or pulsatile umbilical venous flow;
- Stage IV—presence of ascites, pericardial or pleural effusion, scalp edema, or overt hydrops;
- Stage V—demise of one or both fetuses.

During expectant management of patients with TTTS, one may see no progression from one stage to the next, sequential change, or non-sequential progression of disease. Regardless of whether or not the disease follows an orderly pattern, the proposed staging system has prognostic value [4].

Fetoscopic Laser Therapy

Inclusion criteria

Since the first randomized trial on interventions for TTTS, comparing laser to amnioreduction, was published [10], it has been recognized that first-line treatment for all stages of TTTS diagnosed before 26 weeks is laser treatment. However, since laser treatment has only been advocated in a few specialist centers [6], and < 10% of pregnancies in the aforementioned study were in Quintero stage I or IV [10], it is premature to conclude that laser coagulation should be the first-line treatment in all cases [22]. For stage I cases in particular, Quintero et al found that the prognosis was not significantly different between stage I TTTS treated by amnioreduction and that treated by laser therapy [23]. It is possible to follow stage I TTTS patients expectantly as long as the degree of polyhydramnios is not severe (MVP, 8–9 cm) and the cervical length is adequate (> 2.5 cm), especially when the disease is diagnosed after 22–24 weeks of gestation. Such pregnancies have a great chance of remaining stable and not requiring invasive therapy [4].

The advantage of laser treatment for stage I TTTS is that 95% of cases need only one procedure, as opposed to cases treated by serial amnioreduction that usually require multiple tappings. Therefore, laser treatment may be a good alternative choice for early-onset stage I TTTS if patients do not wish to receive multiple invasive procedures as their pregnancy progresses.

In Chang Gung Memorial Hospital, we currently recruit TTTS patients for laser operation using the following inclusion criteria: (1) Stage II, III and IV TTTS with gestational age < 26 weeks; (2) Stage I TTTS with gestational age < 22 weeks.

Contraindications

Not all TTTS cases are suitable candidates for laser therapy. Cases with gestational age > 26 weeks when fetuses are viable are not offered the fetoscopic surgery option due to the invasiveness of the procedure itself. Other contraindications for laser surgery include

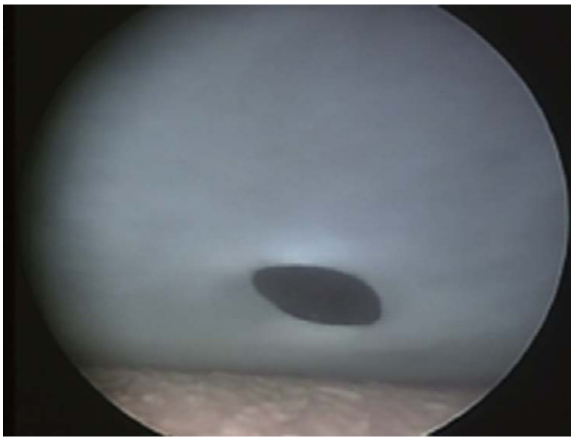

Figure 1. Septostomy after amniocentesis.

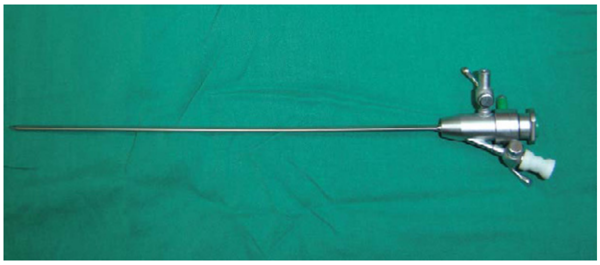

Figure 2. A 0' fetoscope with working sheath.

abnormal genetic studies, ruptured or detached membranes, prior septostomy (a hole in the dividing membrane; Figure 1), short (defined as < 2.5 cm) or dilated cervix, preterm labor and placenta previa. Short cervix and placenta previa are recognized as relative contraindications to laser surgery. In cases with severe TTTS but with short cervix, postoperative cerclage of the cervix is important.

If the distance of umbilical cord insertion of the two involved fetuses is short, the communicating vessels would be too large for photocoagulation. For fetal surgeons fresh in this field, such cases may be difficult for them to handle. Quintero and his group have dealt with cases of total anterior placenta and short distance between the two cords in the two involved fetuses using laser operation with great skill; even in cases with detached membranes, they could perform laser therapy with or without the help of amniopatch [24]. For an old hand with great familiarity and maturity of skill, more difficult cases can be managed. New fetal surgeons, however, should take great care in selecting TTTS cases for fetoscopic laser therapy so that they do not end up with cases that are beyond their capacity or experience.

Fetoscope

Several manufacturers have developed equipment that is specifically designed for fetal surgery. Currently, the experience gathered with any type of fetoscope is limited and there is no evidence that any one particular brand of endoscope performs better than another [25]. The main difference of design may lie in the way the working channel fits in. In some brands of fetoscope, the working channel is built within the scope itself (such as that from Richard Wolf GmbH, Knittlingen, Germany), whereas in others, the working channel is attached to the sheath (such as that from Karl Storz GmbH & Co. KG, Tuttlingen, Germany; Figure 2). The advantage of placing the working channel within the scope is that there is no need to move the sheath during operation, thus reducing the risk of tearing the membrane, while the disadvantage is that the space within the scope is limited due to sharing with the working channel, thereby decreasing the scope's field of vision. There are different strategies for approaching the anterior placenta. Some use curved or angled scopes [19]. In Storz's designation, the laser fiber can, through a special design, be curved, but at the cost of fitting in a larger sheath (3.7 mm) as compared with a smaller one (2.2 mm) for the posterior placenta. The Wolf design offers a 70° scope to view the placental vessels at a difficult angle but just for diagnosis not for operation.

Laser

We currently use Nd:Yag laser as the energy source to photocoagulate TTTS placental communicating vessels. Nd:Yag laser selectively heats up hemoglobin, so it can, therefore, coagulate the placental vessels well. Because of problems with its stability, however, the high power output Nd:Yag laser machine, usually required to generate output as high as 50 watts, has become less available in recent years. In many other centers, the diode laser is chosen as an alternate energy source for laser treatment [26]. Usually, the diameter of the laser fiber is $< 600\,\mu$ (0.6 cm), so that it can pass through the fetoscopic working channel. From our experience, a $400\,\mu$ fiber can pass through the working channel more freely than a $600\,\mu$ fiber, but some brands of laser machine cannot deliver high power output through a $400\,\mu$ fiber, with some delivering up to 20 watts of energy only.

Ultrasound

During fetoscopic operation, a sonographer or sonographist with a sonography machine should be present in the operating room to assist with the surgery. Sonography not only serves to guide as the fetoscope enters the uterus, but also monitors the status of the fetuses during operation and the amount of amniotic fluid before and after the operation. Smooth cooperation between the sonographist and fetal surgeon is very important for conducting successful fetal surgery.

Preoperative management

Usually, the patient is admitted on the same day as or on the day before the operation. Prophylactic antibiotic is administered routinely in the operating room before laser surgery. Indomethacin suppository 100 mg is given 1 hour before surgery as prophylactic tocolysis. History taking and physical examination to pick up factors that can influence the operation, such as hyperthyroidism and heart murmur, are very important.

Anesthesia

At Chang Gung, we used epidural anesthesia in our first four cases, but one also received spinal anesthesia due to epidural failure. Quintero, however, routinely applied local anesthesia as he performed fetal surgery, while the anesthetic doctor stood by.

Patient position

The position of the patient depends on the placenta site. Supine position is usually sufficient for cases with posterior placenta. In cases with fundal area placenta, placing the patient in a lithotomy position may help to effect a better approach to the communicating vessels.

Procedure

First, identify the possible vessels on the uterine wall, choose a placenta free area, and then apply Doppler mode to detect any vessels on the uterine wall that could hamper the entry of the sheath. Because of polyhydramnios, we usually have no trouble finding a free space to insert the scope. Quintero rarely needed to insert the sheath transplacentally, but nevertheless, according to Yamamoto et al, whether or not the fetoscope is inserted transplacentally has no significant effect on clinical outcome, despite the fact that insertion through the placenta may carry a higher risk of intra-amniotic bleeding [26].

Second, put the sheath and trocar into the uterus in order to enter the recipient sac. If it is mainly posterior wall placenta, then it is usually easy to enter the recipient sac without septostomy, and there is usually no need to put in a special instrument like an angled scope to shoot the communicating vessels. If it is mainly anterior wall placenta, then it is usually more difficult to enter the recipient sac than if the placenta is posterior. In special conditions such as if the free space is at the donor side on entry into the uterus, septostomy may be unavoidable and specially designed instruments are needed to shoot the communicating vessels.

Third, identify the communicating vessels. The rationale for detecting the communicating vessels between the two involved fetuses has been described by Quintero et al [17]. A deep arteriovenous communication from donor to recipient is identified if the artery originates from the donor cord and ends in a cotyledon from which the emerging vein runs towards the cord of the recipient twin. Arteries appear darker in color and can be seen to cross over veins. Superficial artery-to-artery or vein-to-vein anastomoses are also coagulated and are identified as vessels that do not have a terminal end in the placenta, but rather continue their course from one umbilical cord to the other. All vessels are followed systematically from the point they cross the intertwining membrane. This technique allows sparing of vessels that are critical to the donor or the recipient [18]. Under the fetoscope, those vessels that cross over the dividing membrane but, through tracing their course, appear as normal vessels, should be preserved (Figure 3). The communicating vessels are categorized as deep or superficial anastomosis. Deep anastomosis is a placental artery in one fetus connected to a placental vein in another fetus (Figure 4). Superficial anastomosis could be artery to artery (Figure 5) or vein to vein (Figure 6). In Chang et al's series [27], there were about 4.2% of anastomoses that could not be totally coagulated during fetoscopic operation by examining placentae sent back for analysis after delivery. Incomplete coagulation of anastomoses can lead to persistent TTTS, reverse TTTS, dual intrauterine fetal demise or marked isolated discordant hemoglobin levels [28]. In that case, when there is doubt as to whether a vessel is connecting or draining the placenta of only one twin, it is better to coagulate it to minimize the risk of leaving an anastomosis behind.

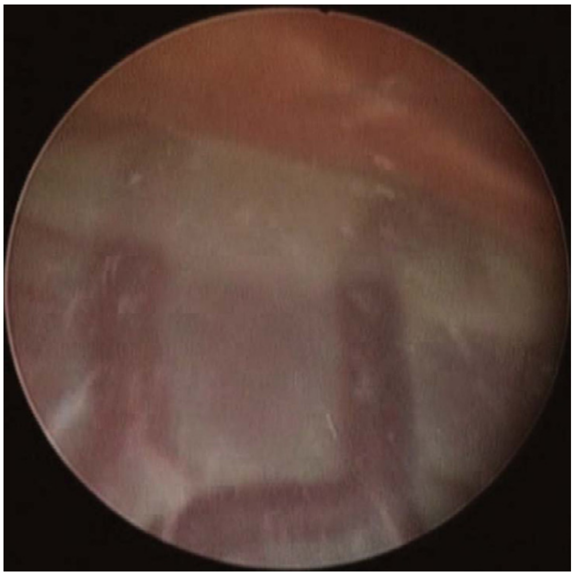

Figure 3. Normal perfused vessels with paired artery and vein.

Fourth, laser photocoagulation is usually started with 15–20 watts. If the gestational age is advanced or the communicating vessels are large, it may be necessary

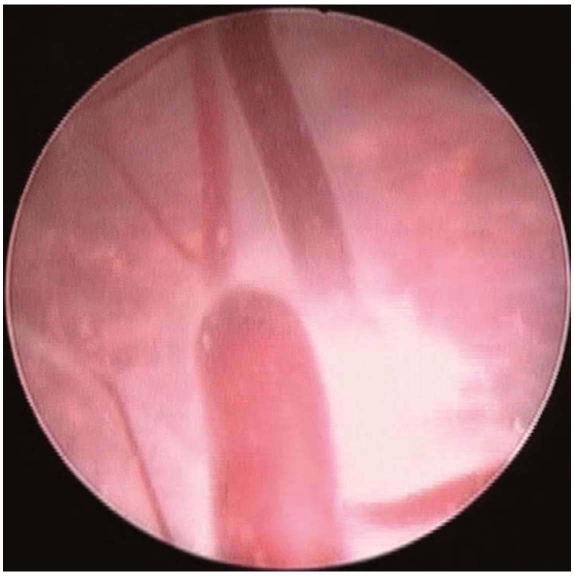

Figure 4. Communicating vessel from donor artery to recipient vein.

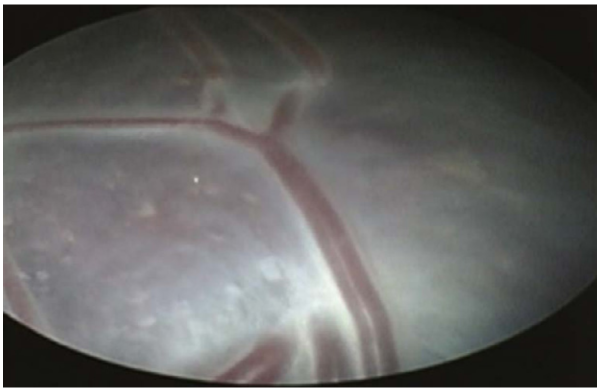

Figure 5. Communicating vessel from donor artery to recipient artery.

to increase the power of the laser to 25–30 watts. We seldom use laser power > 35 watts.

Fifth, amnioreduction is performed by draining the amniotic fluid to leave the MVP < 8 cm.

Sixth, the sheath is pulled out. After the fetoscope and sheath are pulled out of the uterus, the insertion site is checked by sonography for signs of bleeding. If there is bleeding in the uterine wall, compression of the wound from the abdominal wall will usually stop the bleeding.

Seventh, the surgeon then decides whether or not to suture the abdominal wound. Usually, the wound is left without suture.

Prognosis

Survival of at least one fetus has increased from 61% to 83% with a selective technique, and dual fetal losses have decreased from 22% to 5%, with a 4.2% neurologic handicap rate [23].

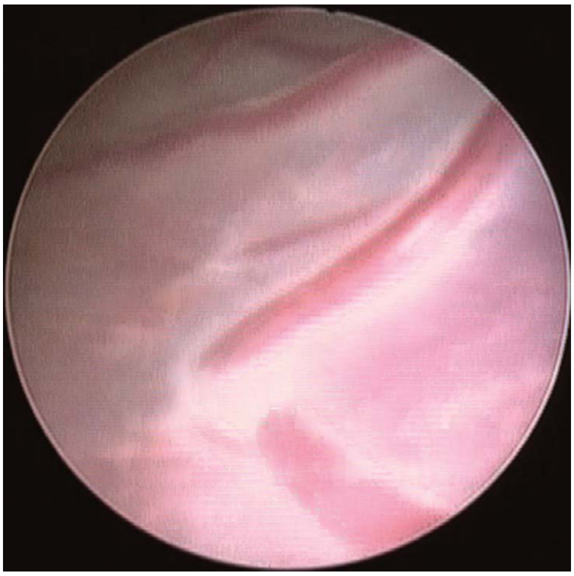

Figure 6. Communicating vessel from donor vein to recipient vein.

Postoperative care

Patients remain in the hospital for 12–48 hours, and complications such as maternal discomfort, vaginal bleeding, premature rupture of membranes (PROM), high temperature, and need for postoperative analgesia have been reported. Cervical length before and after operation are checked; if cervical length < 25 mm, then a cerclage suture is put in. After laser therapy, ultrasound examination should be performed daily during hospitalization. If there are no signs of PROM or infection, and the donor bladder can be visualized, then the patient may be discharged home and receive weekly clinic follow-up.

Complications

All published reports agree that this procedure carries a minimal risk to the mother and that significant maternal surgical complications are rare [9]. No maternal death has been found to be a direct consequence of the procedure. Yamamoto et al reported amniotic fluid leakage into the maternal peritoneal cavity in 13/175 (7.4%) cases and vaginal bleeding in 7/175 (4%) cases after surgery [26]. PROM has been recognized as the most frequent complication of laser therapy. In the Yamamoto et al series, PROM occurred in 49 (28%) patients, at within 1 week of laser therapy, between 8 and 21 days, and after 3 weeks in 7%, 5%, and 17% of the cases, respectively [26].

Follow-up

Patients should be followed-up weekly, whether at the hospital where the surgery was performed or at the primary care hospital. Doppler studies of the middle cerebral artery, umbilical artery, umbilical vein and ductus venosus should be performed at weekly intervals.

Delivery

In TTTS cases that do not receive laser therapy, monochorionic twins are considered to be at high risk for sudden transfusion throughout labor and delivery; therefore, they are generally delivered by cesarean section. In cases of TTTS treated by SLPCV, monochorionic twins are rendered functionally dichorionic, and thus pose no danger for vaginal delivery if no other obstetric contraindications exist.

Placentae should be examined for the site of laser photocoagulation and any remaining residual communicating vessels, if any, that may have escaped detection during operation (Figure 7).

Long-term Neurologic Outcomes of Fetuses Post Laser Treatment

There are reports stating that severe cerebral lesions in TTTS treated with fetoscopic laser surgery are frequent and result mainly from antenatal injury [29]. A 14% incidence of cerebral palsy in cases of TTTS post laser therapy has been reported, as opposed to the 4.2% neurologic handicap rate reported by Chang et al [27]. The number and incidence of residual anastomoses that failed to be coagulated during operation may, for a large part, account for the differences in the incidence of neurologic sequelae. More uncoagulated anastomoses mean more neurologic complications. Early-onset TTTS has a poor prognosis if untreated; 90% of fetuses would not survive [30], let alone appear normal at follow-up.

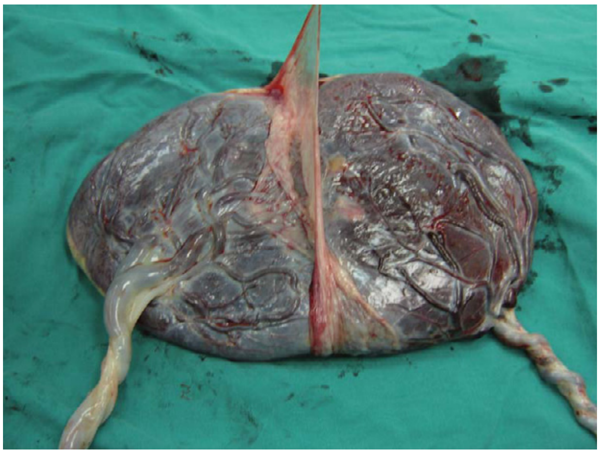

Figure 7. Placenta of twin–twin transfusion syndrome post laser therapy.

Laser treatment dramatically improves the outcome of early-onset TTTS.

Conclusion

Fetoscopic laser therapy for TTTS performed percutaneously before 26 weeks of gestation is a minimally invasive treatment with few maternal complications, with PROM becoming the main source of neonatal complications [26]. Amnioreduction should be offered to advanced stage (stage III and IV) cases only when laser therapy is not available or when gestational age is > 26 weeks. Laser therapy for TTTS can be performed with minimal risk to the mother at centers staffed with well trained maternal–fetal medicine specialists and equipped with efficient instruments.

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